PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 9/20, 9/70	A1	WO 91/16041
		(43) International Publication Date: 31 October 1991 (31.10.91)

(21) International Application Number: PCT/GB91/00651

(22) International Filing Date: 24 April 1991 (24.04.91)

(30) Priority data:
9009390.7 26 April 1990 (26.04.90) GB

(71) Applicant *(for all designated States except US)*: SMITH KLINE & FRENCH LABORATORIES LIMITED [GB/GB]; Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : TOVEY, Geoffrey, David [GB/GB]; SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(74) Agent: THOMPSON, Clive, B.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Pharmaceutical compositions in the form of a wafer for the delivery of medicaments to the sub-lingual mucosa are described.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**ES**	Spain	**MG**	Madagascar
AU	Australia	**FI**	Finland	**ML**	Mali
BB	Barbados	**FR**	France	**MN**	Mongolia
BE	Belgium	**GA**	Gabon	**MR**	Mauritania
BF	Burkina Faso	**GB**	United Kingdom	**MW**	Malawi
BG	Bulgaria	**GN**	Guinea	**NL**	Netherlands
BJ	Benin	**GR**	Greece	**NO**	Norway
BR	Brazil	**HU**	Hungary	**PL**	Poland
CA	Canada	**IT**	Italy	**RO**	Romania
CF	Central African Republic	**JP**	Japan	**SD**	Sudan
CG	Congo	**KP**	Democratic People's Republic of Korea	**SE**	Sweden
CH	Switzerland			**SN**	Senegal
CI	Côte d'Ivoire	**KR**	Republic of Korea	**SU**	Soviet Union
CM	Cameroon	**LI**	Liechtenstein	**TD**	Chad
CS	Czechoslovakia	**LK**	Sri Lanka	**TG**	Togo
DE	Germany	**LU**	Luxembourg	**US**	United States of America
DK	Denmark	**MC**	Monaco		

PHARMACEUTICAL COMPOSITIONS

The present invention relates to a pharmaceutical composition for the delivery of medicaments which are absorbed through the sub-lingual mucosa, and to a method for the preparation of such a composition.

It is known to administer medicaments to the oral mucosa, for example the sub-lingual mucosa. Administration by this route has been used when, as in the case of nitroglycerine and nifedipine, it is desired to cause the medicament to be transported into the bloodstream rapidly in order to achieve a rapid therapeutic effect. Another reason for administering a medicament for absorption by the sub-lingual mucosa, rather than by the intestinal mucosa as is the case with most oral dosage forms, would be the instability of certain medicaments, e.g. peptides or hormones, to the physiological environment in the stomach and intestines. Various types of composition have been disclosed in the art as being suitable for the administration of medicaments to the oral mucosa. Such compositions include aerosol sprays (e.g. Nitrolingual^{TM}), soft gelatin capsules which can be ruptured and then placed under the tongue to release their liquid contents (e.g. Adalat^{TM} soft gelatine capsules), sub-lingual tablets, and various sub-lingual and buccal patches and membranes containing medicaments.

Certain disadvantages are inherent in many of the prior art compositions. Thus, for example, the application to the sub-lingual mucosa of a spray or liquid formulation can be an inefficient means of administering a medicament since much of the liquid will drain away down the throat. Sub-lingual tablets can suffer from the disadvantage of being difficult to retain under the

tongue for a time sufficient to permit adequate absorption of the drug and certain of the buccal patch and membrane dosage forms suffer from the disadvantage of technical complexity and, moreover, are not edible, that is to say they are not degraded readily in the body and must be removed from the mouth for disposal.

There has now been discovered a composition which offers the advantages of cheapness and simplicity of manufacture; which is edible and therefore does not give rise to disposal problems; which is able to conform to the shape of, and adhere to, the mucosa when hydrated by saliva thereby allowing efficient localised delivery of the medicament; and which permits a steady leaching out of the medicament at a rate which allows its efficient absorption across the mucosal membrane, rather than giving rise to a bolus dose much of which is subsequently washed down the throat by salivary juices; and which is shaped to fit more comfortably against the mucosal site of delivery.

In a first aspect, the present invention provides a pharmaceutical composition for the delivery of medicaments which are absorbed through the sub-lingual mucosa, which composition comprises one or more such medicaments and a solid carrier which is a wafer formed substantially from starch, the wafer being of a thickness which permits it to be moulded to the contours of the sub-lingual cavity following hydration with saliva thereby allowing localised delivery of the medicament.

Suitably the wafer has a thickness of 0.3 to 1.0 mm, preferably 0.5 to 0.9 mm.

The dimensions of the wafer must be such that it can be easily accommodated in the sub-lingual cavity.

Suitably the largest dimension of the wafer is between 10 and 40 mm.

For delivery of a medicament to the sub-lingual mucosa a wafer is suitably placed under the tongue whereupon it softens and moulds to the shape of the mucosal surface with which it is in contact. In this position it adheres reasonably well for sufficient time to allow release of medicament to the sub-lingual mucosa. The wafer can be self-administered or administered by a third party particularly in the case of semi- or unconscious patients.

Preferably the wafer is shaped to provide a cut-away region to accommodate the frenum. In particular the wafer is substantially crescent-moon-shaped. Suitable dimensions for such a shape are an overall length of 10 to 40 mm and an overall width of 5-15 mm, particularly 19 mm by 10.5 mm.

Suitably the wafer comprises any pharmaceutically acceptable starch such as maize, wheat, potato, rice or soya starch or mixtures thereof together with water and optionally a lubricant or emulsifier such as soya starch or a suitable vegetable oil such as rape seed oil. If desired the starch may be pregelatinised. Preferably the wafer is formed from rice paper which may be obtained from G.T. Culpitt & Son Ltd., Wheathampstead, Herts., England.

Such rice papers suitably comprise:

	% w/w
Water	5.0 - 20.0
Starch	80.0 - 95.0
Lubricant	0 - 0.5
Emulsifier	0 - 0.5

The pharmaceutical compositions of the present invention comprise any medicament which can be absorbed through the sub-lingual mucosa, in particular a medicament which is unstable in the physiological environment of the stomach or intestines or which has diminished oral bioavailability due to first past metabolism via the liver. Examples of such medicaments include prostaglandins, vaccines, peptides such as a growth hormone e.g. human growth hormone, or a calcitonin, nicotine, nifedipine, auranofin, fenoldopam, glyceryl trinitrate and other compounds for the treatment of angina. A unit dose suitably comprises no more than 50 mg of medicament preferably no more than 25 mg.

By the term 'a calcitonin' is meant both naturally occurring calcitonins or derivatives and analogues thereof. Examples of naturally occurring calcitonins include human calcitonin (CAS RN : 21215-62-3), rat calcitonin (CAS RN : 11118-25-5), salmon calcitonin (CAS RN : 47931-85-1), eel calcitonin (CAS RN : 57014-02-5), reduced chicken calcitonin I (CAS RN : 96157-98-1), chicken calcitonin II (CAS RN : 103468-65-1), ox calcitonin (CAS RN : 26112-29-8), pig calcitonin (CAS RN : 12321-44-7) or sheep calcitonin (CAS RN : 40988-57-6).

Examples of synthetic calcitonins include the des-[Ser^2, Tyr^{22}]-Gly^8-calcitonins described in US-A-4,597,900, the des-[Tyr^{22}]-salmon calcitonins described in US-A-4,304,692, and the 1,7-dicarba-calcitonins such as eel 1,7-dicarbacalcitonin (elcatonin CAS RN : 60731-46-6), salmon 1,7-dicarbacalcitonin (CAS RN : 60864-37-1) and human 1,7-dicarbacalcitonin (CAS RN : 66811-56-1).

Preferred medicaments for use in the compositions of

the present invention include a calcitonin (in particular eel calcitonin or elcatonin), human growth hormone or nifedipine.

Suitably a wafer comprises a therapeutically effective dose of medicament, e.g. 40-200 international units of a calcitonin, 0.25 to 5 units of human growth hormone, 0.5-10 mg of nifedipine, 0.1 to 4 mg of nicotine or 1-6 mg of auranofin. Alternatively, a wafer comprises a suitable fraction of a therapeutically effective dose of medicament, necessitating the sequential administration of an appropriate number of wafers to provide the desired dose.

The compositions may comprise other excipients such as flavouring agents, absorption enhancers, e.g. a glycyrrhizinate such as ammonium glycyrrhizinate or stability enhancing excipients e.g. protease inhibitors or mixtures thereof.

In one embodiment a hydrogenated oil or fat is applied to one side of a wafer to render that side hydrophobic. Alternatively this could be achieved by chemical treatment, such as silylation. This has the effect of keeping the medicament within the wafer when it is placed in the mouth with the other side of the wafer adjacent to the sub-lingual mucosa allowing the medicament to be adsorbed therefrom. Preferably the wafer would be marked so that a patient would know which side should be placed in contact with the underside of the tongue.

In a further aspect the present invention provides a process for preparing a pharmaceutical composition as hereinbefore defined which comprises bringing into association one or more medicaments with the carrier.

This can be achieved by the following general methods:-

(1) The medicament can be incorporated within the wafer mix prior to forming the wafer. Suitably an aqueous slurry of the wafer ingredients is prepared in a stainless steel tank using a homogeniser. A known portion of the slurry is then injected onto the base plate of a flat press. Both base and top plates are heated to a temperature of about 170-200°C. The top plate is brought down and the slurry is cooked for a suitable time, e.g. 20 seconds. The cooked wafer sheet is removed by vacuum suction and transferred to a curing oven. A suitable combination of temperature and controlled humidity (e.g. 25°C and 90% Relative Humidity) are used in the oven to cure the wafer sheet, typically overnight. The cured sheet can then be cut into the desired wafer dosage form shapes using a suitable cutting device. The addition of medicaments to the mix would be at a level which would give the correct total dose in the area of wafer cut from the final sheet as the sub-lingual dosage form.

(2) The wafer without medicament can be formed as a sheet (or continuous roll) and then passed through a screen printer or other printer type of arrangement (e.g. as described in US-A-4322449) to apply the medicament as a layer on and/or partly absorbed into, the wafer. The wafer sheet may be simultaneously warmed so as to drive off the solution carrier which suitably is water, alcohol or chloroform. The final dosage form is then cut from the dried wafer. The coat is applied at a concentration appropriate for final dose relative to area of the wafer.

(3) As 2 above but the medicament is applied in the form of a spray in a suitable volatile solvent such as water or chloroform.

(4) To the basic sheet (or roll) of wafer without medicament is applied a solution of the medicament by droplet addition or spraying onto a small area contained within the boundary of each of the final wafer dosage units. The individual dosage units can then be cut from the sheet in the usual manner. This process minimises drug losses and is suitable for expensive compounds such as peptides.

(5) The active wafer may be prepared by immersion of a wafer in a medicament solution, the wet wafer being then placed and thereby 'wet sealed' onto a larger wafer section formed to suit the sub-lingual cavity. Size and weight of the active wafer and the solution medicament concentration are such that the required dose is prepared.

In these methods the medicament can be applied uniformly or, where appropriate, concentrated near the inner edge of a crescent-moon-shaped wafer which, when administered, is then close to the base of the tongue.

If desired the medicament could be applied to the wafer with a dye.

The following Examples serve to illustrate the present invention.

EXAMPLE 1

Preformed rice paper wafers supplied by G.T. Culpitt & Son Ltd. and having the following composition (85.3% maize starch, 4.5% pregelatinised wheat starch, 0.2% vegetable oil and water 10%) were impregnated with nifedipine by a metered-dose solvent application method as outlined below. The method also permits the inclusion of dispersion adjuvants such as Polyethylene

Glycols (PEG).

(a) Minimisation of Nifedipine Exposure to Light

Nifedipine is light sensitive, especially in solution. Minimise exposure to light by carrying out all operations under the minimum level of diffuse reflected yellow light from a source of the appropriate wavelength characteristics.

(b) Preparation of Nifedipine Solution

Dissolve the nifedipine in chloroform, to give a 2.5% w/v solution, by gentle stirring over two or three minutes. If required the PEG can then be dissolved in the nifedipine solution. (15% w/v PEG 3400 can be used to prepare nifedipine/PEG wafers.) The solutions are made up to final volume with chloroform.

(c) Wafer Impregnation

Precut wafer sections substantially crescent-moon-shaped (19 mm x 10.5 mm x 0.8 mm) are held by tweezers. Using a validated micropipetting device 100 microlitres of nifedipine solution is applied as evenly as possible to the surface of a wafer. The impregnated wafer is then dried in air until no discernible odour of chloroform remains. A representative number of wafers from each batch are assayed for nifedipine content and residual solvent levels using high performance liquid chromatography.

EXAMPLE 2

Calcitonin Wafer

A solution of elcatonin (160 i. units) in 25 microlitres of water was applied to the surface of a precut wafer section (of the type described in Example 1) with an adjustable micropipette set at 25 microlitres. The wafer was allowed to dry under ambient conditions. Wafers so prepared are packed into aluminium foil or blister packs ready for subsequent use.

Claims:

1. A pharmaceutical composition for the delivery of medicaments which are absorbed through the sub-lingual mucosa, which composition comprises one or more such medicaments and a solid carrier which is a wafer formed substantially from starch, the wafer being of a thickness which permits it to be moulded to the contours of the sub-lingual cavity following hydration with saliva thereby allowing localised delivery of the medicament.

2. A composition according to claim 1 wherein the wafer has a thickness between 0.3 and 1.0 mm.

3. A composition according to either claim 1 or claim 2 wherein the largest dimension of the wafer is between 10 mm and 40 mm.

4. A composition according to any one of claims 1 to 3 wherein the wafer is shaped to provide a cut-away region to accommodate the frenum.

5. A composition according to claim 4 wherein the wafer is substantially crescent-moon-shaped.

6. A composition according to any one of claims 1 to 5 wherein the wafer is formed from any pharmaceutically acceptable starch, water and optionally a lubricant or emulsifier.

7. A composition according to any one of claims 1 to 6 wherein the wafer is formed from rice paper.

8. A composition according to any one of claims 1 to 7 wherein the medicament is a calcitonin, human growth hormone or nifedipine.

9. A composition according to any one of claims 1 to 8 further comprising a flavouring agent, an absorption enhancer, or a stability enhancing excipient or mixtures thereof.

10. A composition according to any one of claims 1 to 9 wherein a hydrogenated oil or fat is applied to one side of the wafer to render that side hydrophobic.

11. A process for preparing a pharmaceutical composition according to claim 1 which comprises bringing one or more such medicaments into association with the carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/00651

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 9/20, A 61 K 9/70

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	GB, A, 2022999 (G.T. CULPITT & SON LTD) 28 December 1979 see the whole document	1,6,7,9,11
Y		2-5,8,10
A	GB, A, 2085299 (ENGLISH GRAINS LTD) 28 April 1982 see the whole document	1-11
Y	DE, C, 871821 (ANGELMI) 26 March 1953 see the whole document, in particular page 2, lines 31-35,42-47	4,5,10
Y	FR, A, 2571253 (NIPPON KKK et al.) 11 April 1986 see the whole document, in particular page 2, line 25, page 8, lines 16,17	2,8

./.

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st June 1991	14. 08. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	FR, A, 2514642 (SANDOZ) 22 April 1983 see page 8, line 34 - page 9, line 11; claims	3

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9100651

SA 46781

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2022999	28-12-79	None	
GB-A- 2085299	28-04-82	None	
DE-C- 871821		None	
FR-A- 2571253	11-04-86	JP-A- 61085315	30-04-86
		CA-A- 1263312	28-11-89
		DE-A- 3534981	10-04-86
		GB-A,B 2166348	08-05-86
		NL-A- 8502697	01-05-86
		SE-B- 462580	23-07-90
		SE-A- 8504580	05-04-86
		US-A- 4777046	11-10-88
FR-A- 2514642	22-04-83	CH-A- 653550	15-01-86
		DE-A- 3237945	05-05-83
		GB-A,B 2108841	25-05-83
		JP-A- 58079916	13-05-83